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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,302	05/31/2005	Pasqua Anna Oreste	GRT/3687-101	7086

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EXAMINER	
BLAND, LAYLA D	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,302	ORESTE ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-134* is/are pending in the application.

4a) Of the above claim(s) *71-89,110-131 and 134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-93,108,109,132 and 133* is/are rejected.

7)☒ Claim(s) *94-107* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/4/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 4, 2010 has been entered.

This Office Action is in response to Applicant's request for continued examination (RCE) filed January 4, 2010, and amendment and response to the Final Office Action (mailed June 29, 2009), filed January 4, 2010 wherein claims 90, 94, 106, and 107 are amended.

Claims 71-134 are pending. Claims 71-89, 110-131 and 134 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 16, 2008. Claims 90-109, 132, and 133 are examined on the merits herein.

Applicant's amendment to the specification submitted January 4, 2010 to correct an obvious error in theoretical molecular weight calculation is acknowledged.

In view of Applicant's amendment submitted January 4, 2010, the rejection of claims 103 and 107 under 35 U.S.C. 112, second paragraph, as being indefinite with respect to the definition of LMW and the structure of formula III'b are withdrawn. Applicant's arguments are persuasive.

Upon further consideration, the rejection of claims 94-107 under 35 U.S.C. 103(a) as being unpatentable over Casu in view of Leali is withdrawn. Claims 94-107 require products which are at least 40% or 50-80% 3-O-sulfated in glucosamine units. Case teaches only 20% or 30% sulfation at that position, and Leali teaches that 70-100% of the total sequence lacks sulfation at that position (so maximum of 29% sulfated).

In view of Applicant's arguments submitted January 4, 2010, the rejection of claims 90-93, 108, 109, and 132 under 35 U.S.C. 103(a) as being unpatentable over Casu in view of Leali is modified as set forth below; and the rejection of claim 133 under 35 U.S.C. 103(a) as being unpatentable over Casu in view of Leali and further in view of Oreste is modified as set forth below.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 90-93, 108, and 109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leali (The Journal of Biological Chemistry, Vol. 276, No. 41, Issue of October 12, pp. 37900-37908, 2001, of record) in view of Casu (WO 98/42754, October 1, 1998, of record) and Guo et al. (US 6,388,060, May 14, 2002, of record).

Leali teaches highly N,O-sulfated K5 polysaccharide derivatives [see abstract and Figure 1]. In one example, the degree of sulfation was 3.84 and the molecular weight was 15,000 [Table I]. Angiostatic activity is found in heparin-mimicking, polyanionic compounds [page 37907, second paragraph]. A high degree of sulfation, including N- and 6-O-sulfation of the Glc residues, and also in the 2-O-, 3-O- positions in GlcA residues and 3-O-position in Glc residues are important for activity [page 37907, first column, last paragraph]. The highly N,O-sulfated K5 derivative exerts a potent FGF2 antagonist and angiostatic activity and has low anticoagulant activity, which makes highly sulfated K5 derivatives attractive targets for design of novel therapeutic compounds [page 37907, last paragraph]. The products are prepared using sodium carbonate [page 37901, second column, fifth paragraph], which would be expected to give the sodium salt of the SO_3^- groups.

Leali does not teach epimerized products and the degree of sulfation of Leali's product is 3.84.

Casu teaches products prepared from either K5 polysaccharide or epimerized K5 polysaccharide [page 10, lines 1-8 and claim 8]. The products have a sulfate/carboxyls molar ratio from 2.0 to 3.5 and molecular weight of 1,500-8,000 or 8,000 to 18,000, or 8,000 to 25,000 [claims 1-5]. The epimerized products are 30:70 or 60:30 iduronic acid to glucuronic acid, which is similar to commercial heparin sulfate [page 10, lines 1-7]. The products are prepared using sodium acetate [page 11, part d], which would be expected to give the sodium salt. Casu also teaches that low molecular weight heparins have lower anticoagulant activity and better bioavailability compared to traditional

heparins [page 2, lines 10-21]. Supersulfated glycosaminoglycans can be prepared by methods known in the art [page 4, lines 15-18].

Guo teaches methods of preparing highly sulfated uronic acid-containing polysaccharides [see abstract]. Heparinoids having a degree of sulfation of 4 can be obtained using the process [column 3, lines 15-22].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare Leali's products from epimerized K5 polysaccharide and to prepare products having a degree of sulfation up to 4. Leali teaches that the activity of the compounds is due to the heparin-mimicking, polyanionic structures. Casu teaches that epimerized and non-epimerized K5 polysaccharides can be used interchangeably. Thus, the skilled artisan would expect epimerized and non-epimerized products to have similar activity. Furthermore, epimerized products are closer in structure to heparan sulfate, as taught by Casu. Since Leali teaches the desirability of heparin-mimicking structures and epimerized products are more similar to heparan sulfate, the skilled artisan would expect epimerized products to be effective. Leali teaches that a high degree of sulfation is important for activity, and teaches a product having a degree of sulfation of 3.84, which is very close to 4. The skilled artisan would be motivated to prepare a highly sulfated product because a high degree of sulfation is key, as taught by Leali. Methods for preparing heparinoids having a degree of sulfation of 4 are known in the art, and would be used by the skilled artisan in order to obtain a highly sulfated product which would be expected to have angiostatic properties.

Claims 132 and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leali in view of Casu and Guo as applied to claims 90-93, 108, and 109 above, and further in view of Doshi (US 5,798,356, August 25, 1988).

Leali, Casu, and Guo teach as set forth above but do not teach compositions containing pharmaceutical or cosmetic compositions.

Doshi teaches compositions comprising angiostatic compounds [see abstract]. Compositions for oral administration [column 10, Example 3] and compositions for topical dermatological administration [column 11, Example 7] along with appropriate excipients are taught.

It would have been obvious to one of ordinary skill in the art to combine the compounds as discussed above with a pharmaceutical or cosmetic excipient. The products have biological activity and so it would be obvious to combine the products with an excipient for administration to a subject. Doshi teaches that angiostatic compounds can be administered orally or topically. It is considered that a composition for topical dermatological administration contains excipients which are suitable for cosmetic use.

Claims 94-107 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In the response dated January 4, 2010, Applicant requests rejoinder of withdrawn claims 71-89, 110-131, and 134 upon allowance of an elected product claim. It is noted that, in order to be eligible for

rejoinder, a claim to a nonelected invention must depend from or otherwise require all the limitations of an allowable claim. A withdrawn claim that does not require all the limitations of an allowable claim will not be rejoined. See MPEP 821.04(b).

Response to Arguments

Applicant's arguments are addressed here to the extent that they are relevant to the new ground of rejection.

Applicant argues that the claimed products have antiviral activity and lack anticoagulant activity, unlike Casu's products, and these properties would not be expected by the skilled artisan. This argument is not persuasive because the skilled artisan would be motivated to modify Leali's compound in order to achieve a compound with angiostatic properties. The angiostatic properties are due to the high degree of sulfation, as taught by Leali. Thus, the skilled artisan would expect that a highly sulfated compound would retain the angiostatic properties. Leali also teaches that the highly sulfated product has low anticoagulant activity compared to heparin. Although Leali is silent with respect to antiviral activity, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). As taught by Baba et al. (The Journal of Infectious Diseases 1990; 161:208-213), sulfated polysaccharides are known to have antiviral activity which is independent of antithrombin activity. The skilled artisan would have a reasonable expectation for

achieving the claimed products, as set forth above, and would have a reasonable expectation that the products would retain the angiostatic properties taught by Leali.

Applicant argues that it is not so easily possible to replace a non-epimerized product with an epimerized product. This argument is not persuasive because methods for epimerizing K5 polysaccharide are well known in the art, and Casu clearly teaches the use of an epimerized product. As noted in the instant specification, C5-epimerization with C5-epimerase is taught in several references such as WO 92/17507, WO 96/14425, WO 97/43317, WO 01/72848, and US 2002/0062019. Thus, it is considered within the skill of the skilled artisan to obtain epimerized starting materials such as those used by Casu.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Bland/
Examiner, Art Unit 1623